

REMARKS**A. The objection to the specification has been overcome**

The Examiner objected to the amendment to the paragraph beginning at page 4, line 26, asserting that incorporation of the names of the 46 non-essential genes of herpes simplex virus was an improper incorporation by reference of essential matter. The Examiner further asserted that “the new material added to the specification is ‘essential material’” Office Action at page 3. In response, Applicants traverse.

The application-as-filed expressly stated that “[v]iruses lacking internal repeated can be further attenuated if necessary by the deletion of one or more of the 47 genes found dispensable for viral replication in culture [Roizman, *Proc. Natl. Acad. Sci. (USA)* 1996)].” Specification, page 5, lines 12-15. In the amendment mailed November 15, 2004, Applicants amended the number of nonessential genes from 47 to 46 to correct a typographical error that would have been obvious to one of skill in the art upon a consideration of the Roizman reference cited in support of the assertion.

The Examiner identified as assertedly new matter the naming of the 46 nonessential genes of HSV. Applicants submit that the assertedly new matter is merely the names of the 46 nonessential genes of HSV. As noted above, the application-as-filed expressly stated that viruses could be further attenuated by deletion of one or more of the genes found dispensable for viral replication in culture. One of skill in the art would understand that an HSV gene dispensable for viral replication in culture is a nonessential HSV gene. Therefore, the original application described the invention as including viruses lacking one or more nonessential genes of HSV. That is not new matter, and Applicants acknowledge that the Examiner has not asserted otherwise. At issue, then, is whether the names of the nonessential genes is new matter that is essential to the claimed subject matter. The 1996 Roizman reference cited in the relevant passage of the application-as-filed (*see* above), however, provides the names of those 46 nonessential genes of HSV, establishing that the names of the nonessential genes of HSV were well known in the art as of the February 5, 1999 priority date claimed in the instant application. The recitation of the names of all of the nonessential genes of HSV is synonymous with the recitation of those genes

nonessential to HSV, merely providing an alternate form of identifying those genes, as would be understood by one of skill in the art. Accordingly, the amendment to the specification in the paragraph beginning at page 4, line 26, does not involve an attempt to add essential matter by incorporation from a non-patent publication in violation of M.P.E.P. § 806.01(p). The objection to the specification for an assertedly improper incorporation by reference has been overcome and should be withdrawn.

B. The rejections for indefiniteness have been overcome and/or rendered moot

Claims 1-4 and 15 were rejected under 35 U.S.C. § 112, second paragraph, as assertedly indefinite in reciting “non-natural protein.” In support, the Examiner asserted that “non-natural protein” could mean a protein that is not encoded by wild-type HSV, a protein that incorporates “non-natural” or unconventional amino acids, or something completely different than either of these options. Office Action at pages 3-4.

Applicants submit that “non-natural protein” has a settled meaning in the art of a protein not found in nature. In the present context, one of skill in the art would understand that placing a “non-natural protein coding sequence under the control of a herpes simplex virus promoter” meant that the encoded protein was not a protein expressed by HSV in nature. Consistent with that understanding, Applicants have noted and the Examiner has acknowledged the recitation in the specification at page 5, lines 6-10, that viruses according to the invention may have alterations that result from placing protein-encoding sequences under the expression control of an HSV α , β , or γ promoter. Reinforcing the meaning of “non-natural protein” as used in the present application is the recitation in the application-as-filed that “viruses . . . may be further altered by the addition of cytokines, as well as enzymes that activate prodrugs.” Specification, page 5, lines 18-20. One of skill in the art would recognize, for example, that cytokines are naturally produced proteins in various cells, consistent with the ordinary meaning of “non-natural protein” in this context as referring to a protein being expressed from a promoter, i.e., an HSV α , β , or γ promoter, from which it is not naturally expressed in nature. In exemplifying “cytokines” and “enzymes,” moreover, the application clarifies that a “non-natural protein” was not limited to a protein having at least one unconventional amino acid. Thus, Applicants maintain their position that “non-natural

protein” is not indefinite in the context of the claimed subject matter. To expedite prosecution, however, Applicants have canceled claim 15, thereby rendering moot the rejection of that claim as indefinite under § 112, second paragraph.

The Examiner also rejected claims 1-4 as indefinite in embracing the subject matter of assertedly indefinite dependent claim 15. Applicants submit that the rejection of claims 1-4 on this basis was improper. The assertedly indefinite term, “non-natural protein,” is not recited in any of claims 1-4. In considering whether each of claims 1-4 complies with 35 U.S.C. § 112, second paragraph, it is the language of each of those claims, and no other language, that is considered. The Examiner has not identified any language in any of claims 1-4 that render vague or ambiguous any limitation of those claims such that the subject matter of any of those claims is unclear. Although Applicants maintain that dependent claim 15 is not indefinite in reciting “non-natural protein,” even if the recitation of “non-natural protein” in claim 15 were indefinite, that fact would have no bearing on the definiteness of the language of claims 1-4. By way of analogy, imagine that any of claims 1-4 were drawn to subject matter graphically represented by a rectangle of fixed dimensions, and dependent claim 15 were drawn to a portion of that subject matter defined by a line approximately dividing the rectangle into equal halves, with the subject matter of claim 15 represented by the area of the newly formed rectangle to the left of the bisecting line. Even if that bisecting line were not precisely fixed, thus providing a basis for arguing that the subject matter of claim 15 were indefinite, that issue is irrelevant to whether any of independent claims 1-4, drawn to the fixed and definite larger rectangle, were indefinite. Stated in the language of the pending claims, even if, contrary to Applicants’ position, “non-natural protein” could be established as an indefinite term in the present context, none of claims 1-4 recites that term. Claims 1-4, in not being limited to “non-natural protein,” include both natural and non-natural proteins. Where the line between natural and non-natural proteins is drawn is irrelevant to the issue of the definiteness of each of claims 1-4. Because the sole basis for rejecting claims 1-4 as indefinite under § 112, second paragraph, was the indefiniteness of language in dependent claim 15, the basis for rejecting claims 1-4 under § 112, second paragraph, was defective and should be withdrawn.

C. The rejection of claims 1-5 and 15 for lack of enablement should be withdrawn

1. Claims reciting, or embracing, “non-natural protein”

The Examiner rejected claims 1-5 and 15 for lack of enablement under 35 U.S.C. § 112, first paragraph, asserting that support could not be found for each of the non-essential genes recited in claim 5. Addressing claim 15, the Examiner stated that the claimed subject matter requires insertion of a “non-natural protein coding sequence” and support for such a vector could not be found. With respect to claims 1-4, the Examiner stated that:

“claims 1-4 are independent claims from which claims 5 and 15 depend. Therefore, claims 1-4 must be broader than claim 15 and encompass all limitations of the dependent claim. For this reasons, claims 1-4 are also rejected as encompassing the limitations for which there insufficient support found in the specification.” Office Action at page 5.

In response, Applicants traverse. With respect to claim 5, Applicants refer to the remarks found in Section B, above, which are incorporated herein by reference. In brief, support for deleting any of the 46 non-essential HSV genes is found in the recitation at page 5, lines 12-15 of the application-as-filed. That statement, that viruses can be further attenuated by deletion of one or more genes found dispensable for viral replication in culture, provides express written descriptive support for deleting any non-essential HSV gene known in the art. Each of the 46 genes recited in the claim was known in the art to be a non-essential HSV gene, moreover, as evidenced by the 1996 Roizman publication cited for that proposition in the application-as-filed (Specification, page 5, lines 14-15). Neither claim 5, nor any other pending claim, attempts to define a subset of non-essential HSV genes, such as a subset that might not have been understood in the art. Rather, claim 5 collectively recites a synonym of one or more non-essential HSV genes in reciting the names of each of those non-essential HSV genes, using names known in the art (*see* the 1996 Roizman publication). Thus, there is no new matter problem with the recitation of the names of these non-essential HSV genes in claim 5 and support for the recitation exists in the application-as-filed at page 5, lines 12-15. Accordingly, the rejection of claim 5 under § 112, first paragraph, for lack of written descriptive support, has been overcome and should be withdrawn. For that reason,

the rejection of claim 5 under § 112, first paragraph, for lack of enablement on the basis of a lack of written descriptive support has also been overcome.

Support for the rejection of claim 15 as lacking written descriptive support was provided in the Examiner's assertion that "support for an HSV vector comprising an insertion of an expressible non-natural protein cannot be found." Applicants continue to disagree with the Examiner, noting written descriptive support is provided at least at page 5, lines 18-20, wherein the application-as-filed recites that "viruses lacking the internal inverted repeats may be further altered by the addition of cytokines, as well as enzymes that activate prodrugs." The written description of an insertion of a coding sequence for any other non-natural protein would not differ from the description provided for cytokines or enzymes, regardless of any functional differences of the encoded proteins. Thus, the written description provided at page 5, lines 18-20, provides a written description of the full scope of the claimed subject matter. Notwithstanding Applicants' position, however, claim 15 has been canceled, thereby rendering moot the rejection of claim 15 under § 112, first paragraph, for lack of written descriptive support, and rendering moot the rejection of claim 15 under § 112, first paragraph, for lack of enablement, based on the asserted lack of written descriptive support.

Applicants' response to the rejection of claims 1-4 under § 112, first paragraph, for lack of written descriptive support, relies on, and herein incorporates, the relevant remarks provided in Section B, above. Although Applicants have established that the limitations added in claims 5 and 15, each of which ultimately depends from independent claims 1-4, are supported by an adequate written description, even if the limitations added in those dependent claims were not supported by an adequate written description, that fact would have no bearing on whether the independent claims satisfied the written description requirement of 35 U.S.C. § 112, first paragraph. The Examiner asserts that the independent claims encompass the limitations of the dependent claims, but that does not mean, and cannot mean, that the independent claims are limited by the limitations introduced in the dependent claims. In assessing whether the written descriptive requirement of § 112, first paragraph, has been met by a given claim, such as any one of claims 1-4, the exclusive focus of the inquiry is on the written descriptive support for the invention as defined in those claims.

None of those claims is limited to subject matter having either a deletion of at least one non-essential HSV gene (claim 5 limitation) or to a coding sequence for a non-natural protein (claim 15 limitation). Thus, this basis for rejecting claims 1-4 under § 112, first paragraph, for lack of written descriptive support is flawed and a *prima facie* case for rejecting these claims on this basis has not been established. Accordingly, the rejection of claims 1-4 on this basis should be withdrawn. Further, the rejection of claims 1-4 under § 112, first paragraph, for lack of enablement based on the asserted lack of written descriptive support has been overcome.

2. The Wands factors

In paragraph 8 of the Office Action, the Examiner rejected claims 1-16 under 35 U.S.C. § 112, first paragraph, for assertedly lacking enablement and supported the rejection by considering factors identified in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). In response, Applicants traverse, and will address each of the Wands factors, in turn, below.

a. The nature of the invention.

The invention involves a therapeutic method for treating tumors that involves administration of a modified Herpes Simplex Virus that is selectively cytotoxic to dividing tumor cells. The invention does not involve gene therapy and does not fall into the realm of gene therapy. The claimed methods do not involve a modification of the genetic complement of the host cell, which is the realm of gene therapy. The methods as claimed do not insert, by addition or substitution, any gene into the host cell genome. The claimed subject matter is drawn to viral therapies for tumors, and Applicants request that the examination focus on the merits of that subject matter.

The nature of the invention is the use of the well-known property of cytotoxic viruses such as HSV to kill cells. That property of viruses in general, and HSV more particularly, is known in the art. Moreover, biological mutants exhibiting altered properties, such as the modified HSV of the invention exhibiting selective cytotoxicity, are not uncommon to the geneticists and medical healthcare providers of skill in the art.

Accordingly, the nature of the invention is the use of mutants to exploit the phenotypic variation of those mutants, an area that has received considerable attention for a number of years. The nature of the invention, therefore, is not unfamiliar to those of skill in the art and does not imply or establish that the claimed subject matter behaves unpredictably.

b. State of the art and predictability

The Examiner's focus is misplaced in asserting that "the relevant art considered gene therapy as a whole to be extremely unpredictable." Office Action at page 8. The claimed subject matter is drawn to methods of treating tumors using modified viruses, i.e., modified HSV. That is not a form of gene therapy. Gene therapy must overcome delivery challenges not present in viral therapies in that gene therapy must deliver the gene to each cell in need of treatment. In contrast, the capacity of viruses to multiply and spread by infection reduces, if not entirely eliminates, that challenge. In addition, the modified HSV used in the claimed methods do not require the delivery and expression of a non-HSV gene to be therapeutically effective, in contrast to the requirements of gene therapy-based therapies. Rather, the claimed methods rely on the ability of HSV to infect and kill cells, with the modification of HSV shaping those natural properties to provide for selective cytotoxicity being exhibited towards dividing cells such as tumor cells.

In addressing the state of the art, the Examiner relied on seven references, which will be addressed in the order presented in the Office Action. Verma et al. (1997) was cited for its recognition that gene delivery via viral vectors must overcome the challenge of an active immune system. The claimed methods, however, involve the use of a modified HSV as a therapeutic, and HSV has long been known as capable of surviving immunological responses. Decades ago HSV was shown to be a neurotrophic virus able to remain dormant within neurons for years prior to entry into the lytic cycle. During this period, HSV remained safely sequestered within host cells, isolated from any immune system response. The generalized comments of Verma et al. (1997) relating to challenges in using any virus as a vector in gene therapy are not informative as to whether the immune system presents a challenge to using modified HSV as tumor therapeutics. In fact, knowledge in the art specific to HSV reveals that one of skill knew that HSV could function in an immunocompetent host.

The Examiner cites Chamber et al. (1995) for the proposition that more precise control of $\gamma_134.5$ expression may yield more effective viral therapeutics. Office Action at page 8. The Examiner appears to be citing Chamber et al. (1995) in support of the predictability in the art. Applicants request clarification of the Examiner's position if that is not the proposition for which Chamber et al. (1995) is cited.

Advani (1998) is cited by the Examiner for its statement that available data from animal experiments "do not predict a high cure rate" for tumor treatment. Office Action at page 8. The pending claims, however, are drawn to methods of treating tumors, not methods of curing cancer. Thus, whether a tumor treatment method will predictably result in a cancer cure is not informative. The Examiner also relied on Advani's statement that "infection alone produced few cures and the majority of infected tumors either grew more slowly or outpaced cell destruction." *Id.* Applicants are uncertain of the meaning of this statement, and of the basis for the Examiner's reliance on it. Nonetheless, even if the claimed methods resulted in "few cures," that alone would not mean that the claimed methods did not have predictably beneficial outcomes, such as a reduction in the rate of tumor growth.

The Examiner next turns to Crystal (1995) for the proposition that "'human are not simply large mice. There have been several examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials.'" Office Action at page 9 (emphasis in Office Action). The quoted statement, however, has to do with gene transfer, i.e., gene therapy, and not with the use of modified herpes viruses in tumor therapies. In fact, the quoted statement does not even make clear that the gene transfer is accomplished with any virus vector, let alone HSV. Finally, safety and efficacy trials may be of interest to governmental regulatory agencies such as the FDA, but the law is well-settled that such concerns are not proper inquiries of the U.S.P.T.O. in assessing patentability.

The Examiner's reliance on Gura was also misplaced. Gura was characterized as disclosing that few drug candidates identified using xenograft models ever made it into the clinic, that "drugs tested in the xenografts appeared effective, but worked poorly in humans." Office Action at page 9 (emphasis in Office Action), and that "animals apparently do not

handle the drugs exactly the way the human body does” (emphasis in Office Action).

Whether drug testing in a xenograft model led to commercial success, clinical trials, or therapeutics that met some subjective threshold of performance in humans are not central issues to the predictability in the art, however. As noted above, clinical success is relevant to the efficacy and safety concerns of the FDA, and does not establish a lack of predictability that a drug operable in treating a tumor in a xenograft model would be operative in treating a tumor in a patient. Gura was not relied upon for stating that drugs tested in xenografts that appeared to be effective did not work in humans, or any other animal. Thus, success in testing using xenograft models correlated positively to efficacy in humans, regardless of the magnitude of the therapeutically beneficial effect. Further, the statement that animals and humans handle the drugs differently is conclusory, based on an apparent difference in response magnitude, not kind.

Kerbel was characterized as disclosing that “[a] recurring problem with the use of present models of transplantable tumors is that they frequently respond to anti-cancer drugs or other therapies which then show no activity in humans” (emphasis in Office Action). Office Action at page 9. In noting that transplanted tumors show an exaggerated response to drugs, reliance on Kerbel is misplaced. At issue is whether xenograft model data is predictive of patient data, and an “exaggerated” response may differ in magnitude, but not kind. Stated in the alternative, an “exaggerated” response relative to a baseline response must be the same kind of response as the baseline response, with the “exaggerated” response being of greater magnitude relative to the baseline response. Thus, the “exaggerated” positive response of xenografts to a drug would be predictive of a beneficial effect of that drug on patients, and a difference in magnitude would not change that fact. The Examiner also relied on Kerbel’s asserted identification of problems with the mouse xenograft model, as enumerated i-iii in the Office Action at pages 9-10. Point i, that drugs are tested at the mouse, not human, threshold for tolerance, is an issue that relates to safety, not operability or predictive power. Point ii, that transplanted tumors typically grow quickly and drugs may show an “exaggerated” response towards transplanted tumors relative to human tumors, again relates to magnitude of response, not the nature of any response. As such, point ii does not affect the power of transplanted tumor data to predict beneficial effects on tumors that have not been transplanted. Point iii, that drug assays using tumor xenografts usually are directed

towards primary tumors rather than secondary metastases, does not state that such drugs, identified by an effect on a tumor xenograft, will have no effect on secondary metastases. Also, point iii of Kerbel as characterized by the Examiner is not relevant to the claimed subject matter, which is drawn to methods of treating cancer, not just secondary metastases. Thus, none of the enumerated problems with xenograft models is informative on the issue of the state of the relevant art and does not affect the capacity of xenograft model data to predict behavior in a non-xenograft context such as a patient with cancer.

c. Claim breadth and direction/guidance

In subjectively characterizing the claims as “very broad,” the Examiner focuses on the route of administration, which is not an essential limitation of the claimed subject matter. The inventors’ contributions, as defined in the pending claims, are methods of reducing tumor mass in patients using HSV having a particular modification, i.e., a modification in an inverted repeat region such that only one $\gamma_{134.5}$ gene is expressed. The route of administration is not essential to the claimed methods because any route of administration known to be suitable for administration of the modified virus to treat the particular tumor may be used. This situation is analogous to a claim for a pharmaceutical composition comprising a polynucleotide having a unique sequence. A claim to such a composition need not, and would not, recite a particular excipient unless that excipient were essential to the function of the composition. A claim to such a composition is not “very broad” simply because it is not limited to a particular, and non-essential, excipient. The present claims, in fact, are precisely tailored to the invention disclosed in the pending application and are not overbroad.

In addressing the guidance factor, the Examiner relies on Muldoon in asserting that intramuscular administration of the modified virus would be ineffective in treating glioblastoma because of the blood-brain barrier. Like the Examiner, one of skill is well aware of the blood-brain barrier and would avoid routes of administration incompatible with delivery of the therapeutic to the tumor to be treated. Under the law, inoperative embodiments that cannot even be identified without experimentation do not inevitably lead to a conclusion that claims are not enabled. Where, as here, one of skill in the art already knows

that not all routes of administration are suitable for treating all tumors, there can be no doubt that a specification need not reiterate such information in order to provide an enabling disclosure.

The Examiner also argues that “there is a lack of reference between the in vivo nude mouse model data [and] results which skilled artisan would expect in humans.” Office Action at page 11. In particular, the Examiner asserts an absence of guidance as to how to modify the treatment in shifting from the immunocompromised mouse to an immunocompetent patient. HSV itself, however, has demonstrated a capacity to avoid eradication by the host immune system, and one of skill in the art has been aware of that fact for some time. There is no reasonable basis for believing that HSV, long-known for successfully infecting immunocompetent hosts, would be rendered fatally immunosensitive simply because delivery was directed by man to treat a tumor.

The Examiner also maintains that “empirical experimentation would be required to determine an effective amount to treat” various tumors. Office Action at page 11. Optimization of dosage is a routine matter for health professionals that is well within the skill of those of ordinary skill in the art. Such experimentation involves routine procedures and, while the activities may involve “empirical experimentation,” that experimentation is not, and never has been, regarded as undue. The issue of optimization of dosage attends every therapeutic method involving delivery of a therapeutic and the inevitable dosage optimizations attending practice of all of those methods, including the many patented methods, involves routine, not undue, experimentation.

d. The quantity of experimentation

The Examiner asserts that the “specification lacks sufficient guidance to surmount the technical difficulties recognized in the art,” and asserts that “the prior art also lacks solutions to overcome the considerable list of obstacles recognized in the field,” thus requiring trial-and-error experimentation to overcome the obstacles. Office Action at page 11. Further, the Examiner asserts that “as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art.” *Id.* The Examiner fails to identify any

of these problems or obstacles, however, and the conclusion that undue experimentation would be required is, thus, unsupported. Even if these problems or obstacles were identified in passages of the Office Action prior to page 11, Applicants have addressed each of the Examiner's positions without recognizing problems or obstacles requiring anything more than routine, and certainly not undue, experimentation. Therefore, Applicants respectfully submit that a minimal quantity of expected experimentation of a routine nature would be required and this factor favors a conclusion that the claimed subject matters are enabled by the application-as-filed.

For all of the foregoing reasons, Applicants submit that a consideration of the Wands factors in the present matter leads to a conclusion that each of claims 1-16 is enabled throughout its full scope by the application-as-filed. A *prima facie* basis for rejecting any of those claims under 35 U.S.C. § 112, first paragraph, for lack of enablement has not been established and, accordingly, the rejection should be withdrawn.

D. The rejection of claims as anticipated by either Advani (1997) or Advani (1998) should be withdrawn

In the Office Action at pages 12-13, the Examiner asserts that the claims are drawn to methods for reducing tumor mass by administering a modified HSV having only one active $\gamma_{134.5}$ gene, with those claims explicitly encompassing the administration of HSV R7020 and treating CNS tumors. The Examiner characterizes Advani (1997), a published abstract, as disclosing the administration of HSV R7020 to athymic mice bearing a human glioma xenograft. Further, Advani (1997) is characterized as stating that “radiation enhanced viral replication as one of the interactive effects of combining IR and attenuated HSV in treating glioma xenografts and a potential therapeutic motif in the treatment of gliomas.” Office Action at page 13 (emphasis in Office Action).

The Examiner relied on Advani (1998) as teaching the same data as Advani (1997), but with more detail. Office Action at page 13. The Examiner asserted that Advani (1998) taught “a number of different experiments” wherein HSV R3616, an HSV not modified in accordance with the present invention, was directly administered to glioma xenografts by itself or in combination with other agents, and tumor volumes were measured

at different time points. *Id.* For all of these experiments concerning HSV R3616, the Examiner cited Figs. 1 and 2 of Advani (1998), which addressed data relating to HSV R3616, but not any data relating to HSV R7020. The Examiner then quoted Advani (1998) as stating that “the experiment was repeated with R7020, another genetically engineered attenuated virus,” (see p. 161, bottom of second column), indicating that the R7020 was also injected into glioma xenografts in a nude mouse model and tumor volume was measured at certain time points.” *Id.*

Applicants disagree with the Examiner’s characterization of Advani (1998). The passage at the bottom of page 161, second column, of Advani (1998), upon which the Examiner relied, recites that, “[t]o determine whether the effects of irradiation were specific for $\gamma_{134.5}$ R3616, the experiment was repeated with R7020, another genetically engineered attenuated virus.” That statement, referring to a single experiment, is found in the second paragraph of a section of the paper titled “[v]iral replication in irradiated tumor cells.” Advani (1998) at page 161, second column. In the first paragraph of that section, Advani (1998) describes an experiment to measure the replication of R3616 by exposing tumor xenografts to either the R3616 virus alone, or to the virus and to ionizing radiation. It was to this single experiment that the quoted statement (upon which the Examiner relied) in the next paragraph of Advani (1998) was making reference. Consistently, the results of the experiment with R7020 were provided in Figure 3 of Advani (1998), a figure that appears to be identical to the sole figure provided in Advani (1997). Thus, the experiment involving R7020 that was described in Advani (1998) is the same type of experiment, if not the very same experiment, as described in Advani (1997). That experiment involved the delivery of R7020 to a tumor xenograft, followed by tumor excision and destruction to measure viral titer and thereby assess viral replication. Advani (1998) does not disclose, suggest or imply that any other experiment was performed with R7020, including any experiment in which tumor volume was measured. Thus, while Advani (1998) is a paper that provides more detail than the abstract of Advani (1997), that detail concerns the behavior of HSV R3616, an HSV not within the scope of the modified HSVs described in the present application. Accordingly, Advani (1998) provides no more relevant disclosure than is found in Advani (1997).

In response to Applicants' prior argument that neither Advani (1997) nor Advani (1998) teaches a reduction in tumor mass resulting from administration of HSV R7020, the Examiner asserts that such a reduction would have been inherent in the methods disclosed by Advani (1997) and Advani (1998). Applicants respectfully disagree.

Under the law, the doctrine of inherency provides that a reference that does not expressly disclose each limitation of a claim may nevertheless anticipate the claimed subject matter if the missing subject matter is inherently disclosed. M.P.E.P. § 2112 (IV). For subject matter to be inherently disclosed, it must necessarily be found in the prior art disclosure. *Id.* Mere probabilities are insufficient, and the requirement to optimize conditions for that subject matter to be present are insufficient as a matter of law. *See In re Rijckaert*, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993), *In re Oelrich*, 212 U.S.P.Q. 323,326 (C.C.P.A. 1981). Applicants have consistently noted that Advani (1997) and Advani (1998) do not disclose tumor mass or volume reduction, even in xenograft mouse models of gliomas. Applicants disagree with the Examiner's position that Advani (1997) or Advani (1998) inherently disclose such a tumor mass reduction using HSV R7020. Advani (1997) and Advani (1998) reported measurements of R7020 viral titers and R7020 viral distributions in tumor xenografts upon tumor excision and destruction. Neither Advani (1997) nor Advani (1998) tested any effect on tumor mass or volume attributable to R7020 and, consistently, neither cited reference disclosed experiments to find a dose of R7020 that would result in tumor mass reduction. Although dosage is routinely determined in the art of viral oncotherapy, Advani (1997) and Advani (1998) addressed the research issue of the effect of ionizing radiation on HSV R7020 replication in a tumor xenograft, not the effect of HSV R7020 on tumor mass or volume. Thus, neither Advani (1997) nor Advani (1998) disclosed even the routine experimentation required to arrive at a dose that would result in tumor mass or volume reduction.

One of skill in the art would recognize that there are limits to dosages of a modified HSV, such as R7020, that result in tumor mass reduction. Therefore, dosage must be optimized to ensure tumor mass reduction, and not every dosage of HSV R7020 would be expected to lead to tumor mass reduction. For that reason, tumor mass reduction does not inhere in the administration of R7020, alone or in conjunction with ionizing radiation, to an

athymic nude mouse bearing a glioma tumor xenograft. Accordingly, under the law, neither Advani (1997) nor Advani (1998) inherently discloses tumor mass or volume reduction resulting from administration of HSV R7020. Further, neither cited reference expressly discloses tumor mass or volume reduction resulting from administration of a modified HSV, and there is no disagreement regarding that fact. Therefore, neither Advani (1997) nor Advani (1998) discloses, expressly or inherently, each limitation of any of the pending claims. A *prima facie* basis for anticipation of the claimed subject matter in view of Advani (1997) or in view of Advani (1998) has not been established and the rejection should be withdrawn.

E. The rejection of claims as obvious over either Advani (1997) or Advani (1998) in view of Carroll has been overcome

The Examiner relied on Advani (1997) and Advani (1998) for the disclosures characterized above in the context of addressing the rejection of claims for asserted lack of novelty in view of each of those references. The secondary reference, Carroll, was cited as disclosing the administration of a viral-based therapy to treat non-CNS tumors. In response, Applicants traverse.

To establish a *prima facie* basis for rejecting a claim as obvious over a combination of references, as here, the initial burden is on the Examiner to establish a motive to combine the references, to show a reasonable expectation of success in arriving at the claimed invention upon that combination, and to establish that each limitation of a rejected claim is disclosed or suggested by the combined references. Applicants respectfully submit that the Examiner has not met that initial burden.

The Examiner's reliance on either Advani (1997) or Advani (1998) was misplaced because each of these references failed to inherently disclose the reduction of a tumor mass or volume by administering HSV R7020, a modified HSV, as established in Section D, above. The defect in Advani (1997) and Advani (1998) is not remedied by Carroll, and the Examiner has not contended otherwise. Thus, considering either Advani (1997) or Advani (1998) in combination with Carroll, each of the combinations of references fails to disclose or suggest each limitation of any of the rejected claims.

In addition to the failure of the combined references to disclose or suggest each limitation of any of the rejected claims, there is no proper motive or suggestion to combine either Advani (1997) and Carroll, or Advani (1998) and Carroll. Neither of the primary references, Advani (1997) and Advani (1998), has been shown to disclose or suggest a reduction in tumor mass or volume attributable to HSV R7020, a modified HSV in accordance with the invention. Consequently, the Examiner has not established that either of these primary references discloses or suggests a therapeutic method for treating a tumor using HSV R7020. In view of that failure, one of skill in the art would not be motivated to look to Carroll to adapt the Advani disclosure (either Advani (1997) or Advani (1998)) to treating a non-CNS tumor. Thus, the Examiner has not established a motive or suggestion to combine either Advani (1997) or Advani (1998) with Carroll.

In view of the failure to establish a motive or suggestion to combine the references and a failure to disclose or suggest each limitation of any of the rejected claims even if those references are combined, there can be no reasonable expectation of successfully arriving at the invention in view of either Advani (1997) when considered in combination with Carroll, or Advani (1998) when considered in combination of Carroll.

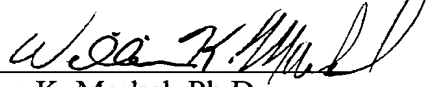
For the foregoing reasons, Applicants submit that the Examiner has not satisfied any of the three requirements for establishing a *prima facie* basis for rejecting any of the claims as obvious under 35 U.S.C. § 103(a) over either Advani (1997) or Advani (1998) when either reference is considered in view of Carroll. Accordingly, the rejection of claims 1-16 has been overcome and should be withdrawn.

F. Conclusion

For all of the foregoing reasons, Applicants submit that all outstanding rejections and objections have been overcome and pending claims 1-16 are in condition for allowance. An early notice thereof is respectfully solicited.

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Respectfully submitted,

By 

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